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Schagen, Frederik H. E.; Hoeben, Rob C.; Hospers, Geke A. P.

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Off-Label Prescription of Genetically Modified Organism Medicines in Europe: Emerging Conflicts of Interest?

Frederik H.E. Schagen,[1] Rob C. Hoeben,[1,2] and Geke A.P. Hospers[1,3]

Abstract

Recently, the first human medicine containing a genetically modified organism (GMO medicine) was authorized for use in the European market. Just as any medicinal product, the market authorization for a GMO medicine contains a precise description of the therapeutic use for which the medicinal product is intended. Within this use, the application of the GMO medicine is permitted, without the need for the institution to obtain a specific permit. In practice, however, medicinal products are also frequently prescribed for treatment outside the registered therapeutic use, a practice that is referred to as ''off-label use.'' While off-label use of conventional medicines is permitted and has been very useful, the off-label use of GMO medicines is not covered in the European Union (EU) legislation or guidelines and falls under each member state's national environmental legislation. This implies that in the Netherlands and most other EU member states, an environmental permit will be required for any institution that uses the GMO medicine outside the registered application(s). In the Netherlands, this permit is identical to the permits required for the execution of clinical trials involving nonregistered GMOs. The application procedure for such permit is time-consuming. This process can therefore limit the therapeutic options for medical professionals. As a consequence, desired treatment regimens could be withheld for certain patient (groups). To make future off-label use of GMO medicines permissible in a way that is acceptable for all stakeholders, regulators should adopt a proactive attitude and formulate transparent legislative procedures for this. Only then the field can maintain the public acceptance of GMO medicines, while maintaining the freedom to operate of medical professionals.

Introduction

THE FIELD OF GENE THERAPY is an illustrative example of a biomedical research field in which the scientific community has been collaborating productively with regulatory authorities in order to develop a rational and reasonable legislative framework for balancing the risks and benefits of the new technology. This has led to a broad public acceptance of the gene therapy field as a viable medical avenue along which to seek new treatment strategies for human disease. In several diseases, evidence of clinical efficacy has been provided, offering hope of new efficacious treatments for serious human diseases that so far were incurable.

Recently, the first human medicine consisting of a genetically modified organism (GMO medicine) was authorized for use in the European market. This GMO medicine, called Glybera, is based on an AAV vector and is developed to treat lipoprotein lipase deficiency (European Medicines Agency, 2012; Bryant *et al.*, 2013). Apart from Glybera, also human vaccines consisting of GMOs, that is, Fluenz and Fluenz Tetra, obtained market authorization within Europe. Both GMO vaccines contain GM-influenza viruses and protect against influenza A and B strains (European Medicines Agency, 2011, 2013).

The market authorization for a medicinal product contains a precise description of the therapeutic indications, dosages, formulations, and patient groups for which the medicinal product is intended. In practice, however, medicinal products are frequently prescribed for treatments outside their registered therapeutic uses, a practice referred to as ''off-label use.'' In the European Union (EU), the drug manufacturers are required to report on the off-label use of their medicinal products as part of the postmarketing surveillance. Physicians are, however, not compelled to notify an off-label prescription and indicated to be not always aware whether a prescription is off-label or not (Caspers *et al.*, 2007).

[1]Netherlands Commission on Genetic Modification (COGEM), 3720 AN Bilthoven, The Netherlands.
[2]Department Molecular Cell Biology, Leiden University Medical Center, 2300 RC Leiden, The Netherlands.
[3]Department Medical Oncology, University Medical Center Groningen, 9700 RB Groningen, The Netherlands.

A systematic analysis of the off-label drug use in outpatient care in the United States revealed that on average 21% of all estimated uses for commonly prescribed medications are off-label (Radley *et al.*, 2006). But the magnitude of off-label use varies widely among specific medications and did exceed 50% for some anticonvulsants, psychiatric medications, and antiasthmatics. Also, in Europe the off-label use is assumed to be common practice. The studies performed to measure its extent focus mainly on the off-label prescription in children. This group is frequently excluded from the registered patient groups. Although the reported percentage off-label use in children is variable, it forms a substantial part of all prescriptions of a registered medicine and can add up to 39% (Conroy *et al.*, 2000, 2003; Jong't *et al.*, 2004; Levêque, 2008). Moreover, a survey of all pediatric uses of medicinal products in Europe, which was issued by the European Medicines Agency, reports even higher rates, especially in case of the drug prescription to prematures, neonates, and infants (European Medicines Agency, 2010).

About a decade ago, the GMO medicinal products Gendicine and Oncorine were approved by the Chinese State Food and Drug Administration for use on the Chinese market (Pearson *et al.*, 2004; Jia, 2006). Both medicinal products were registered for treatment of head and neck cancer, but are extensively off-label-prescribed for the treatment of other tumors, that is, lung cancer, liver cancer, and gastric carcinomas (Ma *et al.*, 2009; Kaptein *et al.*, 2010).

Given the fact that off-label use of conventional medicines is generally accepted and practiced, and the GMO medicines registered in China are widely off-label-prescribed, it seems highly likely that in Europe GMO medicines will be used off-label as well.

Market Authorization of a GMO Medicine Does Not Include Off-Label Use

Before new medicinal products can be authorized for use in the European market, they are put through an extensive evaluation by the European Medicines Agency (EMA) (European Commission, 2006). This evaluation focuses on pharmaceutical quality, efficacy, and safety in view of and limited by the proposed therapeutic indications, dosages, formulations, and patient groups. These are recorded in detail in the Summary of Product Characteristics when a medical product is registered (European Commission, 2009).

Besides evaluating conventional medicines for market registration in the EU, the EMA is also responsible for the evaluation of market authorization applications for medicines partly or wholly based on GMOs. Apart from the efficacy and human safety, the environmental safety forms a key issue in the evaluation of the requested market authorization of a GMO medicinal product (European Medicines Agency, 2009). To ensure the environmental safety, an extensive environmental risk assessment is performed, which is done within the scope of the intended therapeutic use. The possible off-label uses and linked environmental risks are not included in the assessment of the market authorization.

Off-label use of GMO medicines is not accounted for in the EU directives and regulations that are applicable to the market authorization of GMO medicines (The European Parliament and the Council of the European Union, 2001a,b, 2004). Just as conventional medicines, the market authorization of a GMO medicine is limited to the registered therapeutic indications, dosages, formulations, and patient groups. The assessment and the market authorization does not cover off-label use of a GMO medicine. So far, EMA has not issued any guidelines on the off-label prescription of GMO medicines. Consequently, the off-label use of GMO medicines falls under the general European GMO legislation supplemented with each member state's national environmental legislation on the use of GMOs (The European Parliament and the Council of the European Union, 2001a, 2009; Perseus, 2006).

In the environmental risk regulations of the Netherlands and probably of most other member states, the off-label use of a GMO medicine will be considered similarly to a clinical trial, with nonregistered GMO medicinal products. Dependent on the EU member state, this implies that a medical center should apply for a permit for contained use, deliberate release, or, in some countries, for a specific gene therapy trial permit, before starting the off-label use of a GMO medicine (Perseus, 2006).

Prerequisites for Off-Label Use of a GMO Medicine in the Netherlands

Under the Dutch environmental legislation, off-label use of a registered GMO medicine is considered as a deliberate release into the environment. Consequently, the prescription of a GMO medicine for nonregistered therapeutic indications requires a permit for the deliberate release of a GMO into the environment. Such a permit application involves the assembly of a large portfolio of information about the GMO and the biosafety aspects of the study in accordance with the European directive for deliberate release of a GMO into the environment (The European Parliament and the Council of the European Union, 2001a). This includes an assessment of the possibility and impact of dispersal of the GMO and infection of third parties. Also, the potential occurrence of new GMOs as a result of interaction of the GMO medicine with naturally occurring microorganisms is assessed. Dependent on the outcome of the performed environmental risk assessment, the application should identify necessary risk management measures such as containment measures to minimize possible environmental risks.

In the Netherlands, the whole procedure for evaluating the application takes at least 5 months, and longer if the process is interrupted to collect further information or if objections are lodged against issuing the permit during the 6-week period of public consultation (Gene Therapy Office, 2013). Although the permit required for a clinical trial with GMO medicinal products and the procedure followed will differ between the EU member states, the permit application is in general a time-consuming and labor-intensive procedure.

Conflicts of Interest

The off-label prescription of conventional medicines is legally allowed and a common practice in healthcare to date. Dependent on the medicine and its registered therapeutic indication, off-label use can form a substantial share of the total prescription of a medicine. Key criteria for off-label use are a thorough scientific evidence base and the lack of a registered alternative. In practice, off-label prescription is

based on the professional responsibility and the legal obligation of the physician to give the patient an optimal treatment. If off-label prescriptions were prohibited, physicians would be limited in their freedom to offer suitable care to their patients. It would deny patients access to desired treatment, and ''special'' patients, such as children, elderly, pregnant women, and patients with rare diseases, would be left without access to suitable medicines. Off-label use of medicines is therefore essential to provide optimal care to all patients.

On the other hand, we should keep in mind that the interests of the population and the environment are of more importance than those of a relative limited group of patients. In case of the use of GMOs, this requires a careful assessment of the potential impact that the GMOs can have on the environment. Only in this way the environmental risks of the use of GMO medicines can be limited to an acceptable level. However, the relatively lengthy procedure of the environmental permit application may be inhibitive for an off-label prescription. Moreover, since the permits are restricted to a single institution, each hospital needs to repeat the application, even if the off-label use is exactly the same.

The professional responsibility and the obligation of physicians to provide optimal care will put the physician in a dilemma. The physician will be forced to balance the interests of the patient on the one hand, and the interest of the population and the environment on the other. With the recent registration of the first GMO medicine and the GMO vaccines in Europe, the physicians can be faced with this dilemma anytime now.

Quo Vadis?

Although the legislative requirements for the off-label prescription of GMO medicines are clear, they do not do justice to the emerging conflicts of interest. In fact, irrespective of the situation, a physician is legally bound to obtain an environmental permit before any off-label use of GMO medicines is allowed. The question is whether each physician is willing to obey this requirement when there seems to be no eminent environmental risks, and abstain from the obligation to offer the patients the optimal treatment choice.

The Netherlands Commission on Genetic Modification highlighted the possible conflicts of interest in case of the off-label use of GMO medicines already in 2009 (Netherlands Commission on Genetic Modification, 2009). Since then, the first GMO medicine has entered the European market making off-label use of GMO medicines a matter of time. So far, the legislative requirements for this type of off-label prescription remained unchanged, and we have seen no actions being taken to remedy the emerging conflicts of interest. Whereas these conflicts of interest are complex, a balanced solution is required that should meet the interests of the patients, the physicians, and the environment.

One possibility to cope with this issue is to expand the environmental risk assessment beyond the scope of the market authorization application by including, for example, a limited but obvious group of off-label prescriptions in the environmental risk assessment. As part of the assessment of the market authorization application, it could be indicated whether certain off-label uses involve environmental risks comparable with the intended, to be registered use, or entail higher environmental risks. In view of the safety for humans (excluding the patient) and the environment, the first category of off-label uses could be made eligible for a fast-track procedure for issuing the required environmental permit, or even make such a permit no longer mandatory for this category of off-label uses. Obviously, this demands an adjustment of the national and/or European legislation.

Another possibility would be a national central registration of the off-label use of GMO medicines. A central database could give the medical professionals a detailed insight in previously applied off-label uses of GMO medicines. If the intended off-label use has been assessed, there would be no need to repeat this assessment and this should clear the way for a fast-track permit procedure. Moreover, a centralized database would also enable a physician to forward the patient to the hospital with the required permit or to apply for a copy of the permit. This last option is already allowed in the current legislation. In this case, the remaining procedure of evaluating the application remains, however, the same. Obviously, a European-wide central registration could streamline this option even further, but this will only work if the member states conform with a uniform environmental permit for the off-label use of GMO medicines.

Either way, policymakers of involved ministries have to deliberate in close consultation with stakeholders on the practicable policy options and come to a solution that best meet the various interests. If not, it is inevitable that with the off-label use of GMO medicines either the patient interest or the interests of humans and the environment will be jeopardized with all that that entails. In view of the prevailing public opinion on GMOs, it goes without saying that this issue needs the required attention and possible legislative adjustments before the physician is confronted with the illustrated dilemma.

Conclusion

Just as with conventional medicines, it is to be expected that GMO medicines can be prescribed outside their registered therapeutic scope. This might place the medical professional in a dilemma with the patient interest on the one hand, and the public interests of human health and the environment on the other. To ensure that both interests are best served, the regulations need to be adapted in anticipation of the off-label use of GMO medicinal products. If not, the full potential of particular GMO medicines will probably not be exploited and, even worse, might be exploited without proper notification and without a proper environmental risk assessment. In view of the general public perception on GMOs in Europe, the last scenario is risky and may in fact jeopardize the public opinion and acceptance of GMO medicines in general.

This calls for a solution that is fully supported and acknowledged by the medical professionals and might encompass a simplified and accelerated procedure when the environmental risks have been assessed before. With the authorization of the first GMO medicines to the European market, the off-label prescription of this type of medicines becomes a matter of time. Hopefully, policymakers can be incited to address this issue in a timely manner.

Disclaimer

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Author Disclosure Statement

The authors declare that no competing financial interests exist.

References

Bryant, L.M., Christopher, D.M., Giles, A.R., *et al.* (2013). Lessons learned from the clinical development and market authorization of Glybera. Hum. Gene Ther. Clin. Dev. 24, 55–64.

Caspers, P.W.J., Gijsen, R., and Blokstra, A. (2007). Off-label use of prescription drugs: transparency required. RIVM report (370050001). Available at www.rivm.nl/bibliotheek/rapporten/370050001.html (accessed July 2014).

Conroy, S., Choonara, I., Impicciatore, P., *et al.* (2000). Survey of unlicensed and off label drug use in paediatric wards in European countries. European Network for Drug Investigation in Children. BMJ 320, 79–82.

Conroy, S., Newman, C., and Gudka, S. (2003). Unlicensed and off label drug use in acute lymphoblastic leukaemia and other malignancies in children. Ann. Oncol. 14, 42–47.

European Commission (2006). Chapter 4: Centralised Procedure, Volume 2A: Procedures for marketing authorization. Available at http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm (accessed July 2014).

European Commission (2009). A guideline on summary of product characteristics (SmPC), Volume 2C: Regulatory Guideline. Available at http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm (accessed July 2014).

European Medicines Agency (2009). Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products. Available at www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003964.pdf (accessed July 2014).

European Medicines Agency (2010). Report on the survey of all paediatric uses of medicinal products in Europe. EMA report (EMA/794083/2009). Available at www.ema.europa.eu/docs/en_GB/document_library/Report/2011/01/WC500101006.pdf (accessed July 2014).

European Medicines Agency (2011). Product information on Fluenz. Available at www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001101/human_med_001405.jsp&mid=WC0b01ac058001d124 (accessed July 2014).

European Medicines Agency (2012). Product information on Glybera. Available at www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002145/human_med_001480.jsp&mid=WC0b01ac058001d124 (accessed July 2014).

European Medicines Agency (2013). Product information on Fluenz Tetra. Available at www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002617/human_med_001713.jsp&mid=WC0b01ac058001d124 (accessed July 2014).

Gene Therapy Office (2013). Guidelines for investigators and sponsors with regard to the assessment by official bodies of clinical research involving gene therapeutics in the Netherlands. Available at www.loketgentherapie.nl//dsresource?objectid=rivmp:197521&type=org&disposition=inline&ns_nc=1 (accessed July 2014).

Jia, H. (2006). Gene therapy finds welcoming environment in China. Nat. Med. 12, 263–264.

Jong't, G.W., Eland, I.A., Sturkenboom, M.C., *et al.* (2004). Unlicensed and off-label prescription of respiratory drugs to children. Eur. Respir. J. 23, 310–313.

Kaptein, L.C.M., Li, Y., and Wagemaker, G. (2010). Gene therapy in China: from a Dutch perspective. COGEM research report (CGM2011-03). Available at www.cogem.net/index.cfm/nl/publicaties/publicatie/gentherapie-in-china-een-nederlands-perspectief (accessed July 2014).

Levêque, D. (2008). Off-label use of anticancer drugs. Lancet Oncol. 9, 1102–1107.

Ma, G., Shimada, H., Hiroshima, K., *et al.* (2009). Gene medicine for cancer treatment: commercially available medicine and accumulated clinical data in China. Drug Des. Dev. Ther. 2, 115–122.

Netherlands Commission on Genetic Modification (2009). Off-label gebruik van ggo-geneesmiddelen: zegen of zorg? COGEM topic report (CGM/091214-01). Available at www.cogem.net/index.cfm/nl/publicaties/publicatie/off-label-gebruik-van-ggo-geneesmiddelen-zegen-of-zorg (accessed July 2014).

Pearson, S., Jia, H., and Kandachi, K. (2004). China approves first gene therapy. Nat. Biotechnol. 22, 3–4.

Perseus (2006). Analysis of the applicability of the contained use legislation for clinical trials. EC report (070402/2005/419827/MAR/B4). Available at www.eurocobusiness.com/resources/clinical_trial_study_report%20EU.pdf (accessed July 2014).

Radley, D.C., Finkelstein, S.N., and Stafford, R.S. (2006). Off-label prescribing among office-based physicians. Arch. Intern. Med. 166, 1021–1026.

The European Parliament and the Council of the European Union (2001a). Directive 2001/18/EC. Official Journal of the European Communities L 106, 1–38.

The European Parliament and the Council of the European Union (2001b). Directive 2001/83/EC. Official Journal of the European Communities L 311, 67–128.

The European Parliament and the Council of the European Union (2004). Regulation (EC) No 726/2004. Official Journal of the European Union L 136, 1–32.

The European Parliament and the Council of the European Union (2009). Directive 2009/41/EC. Official Journal of the European Union L 125, 75–97.

Address correspondence to:
Dr. Frederik H.E. Schagen
Netherlands Commission on Genetic Modification (COGEM)
P.O. Box 578
3720 AN Bilthoven
The Netherlands

E-mail: erik.schagen@cogem.net

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